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Research Article

SYNTHESIS AND ANTIBACTERIAL SCREENING OF SOME NOVEL N-(3-CHLORO-2-OXO-4-SUBSTITUTED PHENYL AZETIDIN-1-YL) ISONICOTINAMIDE AND 4-(5-SUBSTITUTED PHENYL-1, 3, 4-OXADIAZOL-2-YL) PYRIDINE DERIVATIVES

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ABSTRACT

A new series of N-(3-chloro-2-oxo-4-substituted phenylazetidin-1-yl) isonicotinamide 3(a-j) and 4-(5-substituted phenyl-1, 3, 4-oxadiazol-2-yl) pyridine derivatives 5(a-j) have been synthesized from biologically important Schiff bases 2(a-j), reacted separately with chloroacetyl chloride and acetic anhydride. Schiff bases 2(a-j) were synthesized by reacting isoniazid with different substituted aromatic aldehydes in DMF. The structures of all the synthesized compounds have been elucidated on the basis of their physical, spectral and elemental analysis. The compounds were also screened for their antibacterial activity against *Staphylococcus aureus,Bacillus subtilus*, *Escherichia coli* and *pseudomonas aeruginosa* using ampicillin as standard. The compounds with promising activity have been identified.

Key words: Aromatic aldehydes, Schiff bases, Isoniazid, Antibacterial activity

INTRODUCTION

Azetidin-2-one is of special interest as it is an important moiety associated with the structures of β lactam antibiotics. The biological activity of β lactam antibiotics such as penicillins and cephalosporins are attributed to the presence of 2-azetidinone ring in them. Compounds carrying azetidin-2-one ring are reported to exhibit certain biological effects like antimicrobial[1-5] ,antiinflammatory[6],antitubercular[7],antiviral[8],anticonvulsant[9] and anticancer[10] activities. 1,3,4-oxadizoles are another class of heterocyclic compounds that exhibit diverse biological activities like antimicrobial[11-13],antiinflammatory[14,15],anticancer[16], antiviral[17] and anticonvulsant[18] activities. Hence, in the present work, an attempt has been made to synthesize titled compounds derived from substituted Schiff bases and screen them for antibacterial activity. The reaction sequences for synthesis of title compounds are shown in **scheme-1**.

MATERIAL AND METHODS

Experimental

All the melting points were recorded on Cintex melting point apparatus and are uncorrected. IR spectra in KBr were recorded on Schimadzu FTIR spectrophotometer in cm^{-1}. ^{1}HNMR spectra were recorded in $CDCl_3$ or DMSO on a Bruker DRX-300 MHZ NMR instrument. Chemical shifts were reported in ppm using TMS as internal standard on δ scale. Mass spectra of compounds were recorded on mass spectrometer (Agilant 1100 series). Elemenal analysis was carried out on a Carlo Erba 106 and PerkinElmer model 240 analyzers. Completion of the reactions was monitored time to time by TLC using E-Merck 0.25 mm silica gel plates and chloroform: methanol (9:1) as solvent system.

General procedure for the synthesis of Schiff bases 2(a-j)

A mixture of isoniazid(0.01mol), different substituted aromatic aldehydes(0.01mol) in dry DMF(30mL) was refluxed for 24 hr and the excess DMF(dimethyl formamide) was removed by distillation. Then the mixture was poured into crushed ice with stirring. The solid mass obtained was filtered and recrystallized from ethanol.

General procedure for the synthesis of N-(3-chloro-2-oxo-4-substituted phenylazetidin-1-yl) isonicotinamides 3(a-j)

Chloroacetyl chloride (0.02mol) was added to Schiff base (0.01mol) and triethylamine(0.02mol) in dry 1,4-dioxane(25mL) at 10°C.The mixture was stirred for 24hr.The triethylamine hydrochloride precipitate formed was filtered and washed several times with dry 1, 4-dioxane. The filtrate and washings were mixed and concentrated under reduced pressure. The residue was poured into crushed ice and the crude product obtained was recrystallized from ethanol.

General procedure for the synthesis of 4-(4-acetyl-5-substituted phenyl-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl) pyridine derivatives 4(a-j)

A mixture of Schiff base (0.004mol) and acetic anhydride (10mL) was refluxed for 12hr and left at room temperature for 48hr. The resultant mixture was poured into ice cold water and the solid obtained was filtered and recrystallized from ethanol.

General procedure for the synthesis of 4-(5-substituted phenyl-1, 3, 4-oxadiazol-2-yl) pyridine derivatives 5(a-j)

To a solution of 4-(4-acetyl-5-substituted phenyl-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl) pyridines 4(a-j) in methanol, 10% sulphuric acid was added and refluxed for 2hr. The reaction mixture was cooled to room temperature and then poured into ice cold water. The solid separated was recrystallized from ethanol.

Spectral data

N-(3-chloro-2-oxo-4-phenylazetidin-1-yl) isonicotinamide (3a)

IR(KBr) in cm^{-1}:3384(N-H str), 3032(C-H of aromatic ring), 1729(C=O of azetidinone ring), 1689(C=O str); ^{1}HNMR(DMSO): δ7.66-8.89 (m, 4H, Ar-H in pyridine), 6.88-7.22 (m, 5H, Ar-H), 8.44(s, 1H, -CONH-), 5.34(s, 1H, CH-Cl of azetidinone ring), 3.54(s, 1H, azetidinone proton); MS(m/z):302(M+1).

N-[3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl] isonicotinamide (3b)

IR(KBr) in cm^{-1}:3374(N-H str),3034(C-H of aromatic ring),1732(C=O of azetidinone ring),1676(C=O str),665(C-Cl str); ^{1}HNMR(DMSO): δ7.64-8.85(m,4H,Ar-H in pyridine),6.86-7.20(m, 4H, Ar-H), 8.42(s, 1H, -CONH-), 5.38(s, 1H, CH-Cl of azetidinone ring), 3.56(s,1H,azetidinone proton);MS(m/z):337(M+1).

N-[3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl] isonicotinamide (3d)

IR(KBr) in cm^{-1}:3392(N-H str),3030(C-H of aromatic ring),1726(C=O of azetidinone ring),1669(C=O str),1056(C-O-Cstr);^{1}HNMR(DMSO): δ7.63-8.92(m,4H,Ar-H in pyridine),6.83-7.32(m,4H,Ar-H),8.46(s,1H,-CONH-),5.36(s,1H,CH-Cl of azetidinone ring), 3.86(s,3H,-OCH_3),3.52(s,1H,azetidinone proton);MS(m/z):332(M+1).

4-(4-acetyl-5-phenyl-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl) pyridine (4a)

IR(KBr) in cm^{-1}:3042(C-H of aromatic ring),1676(C=O str),1623(C=N str),1066(C-O-C str); ^{1}HNMR($CDCl_3$): δ7.54-8.62(m,4H,Ar-H in pyridine),6.72-7.34(m,5H,Ar-H), 6.46(s,1H,1,3,4-Oxadiazole proton), 2.86(s,3H,-$COCH_3$);MS(m/z):268(M+1).

4-[4-acetyl-5(4-chlorophenyl)-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl] pyridine (4b)

IR(KBr) in cm^{-1}:3038(C-H of aromatic ring),1678(C=O str),1621(C=N str),1062(C-O-C str),674(C-Cl str); ^{1}HNMR($CDCl_3$): δ7.56-8.64(m,4H,Ar-H in pyridine),6.74-7.32(m,4H,Ar-H),6.43(s,1H,1,3,4-Oxadiazole proton),2.85(s,3H,-$COCH_3$);MS(m/z):302(M+1).

4-[4-acetyl-5(3-nitrophenyl)-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl] pyridine (4c)

IR(KBr) in cm^{-1}:3033(C-H of aromatic ring),1672(C=O str),1623(C=N str),1350(C-NO_2 str),1062(C-O-C str); ^{1}HNMR($CDCl_3$): δ7.52-8.67(m,4H,Ar-H in pyridine),6.72-7.35(m,4H,Ar-H),6.44(s,1H,1,3,4-Oxadiazole proton),2.83(s,3H,-$COCH_3$);MS(m/z):313(M+1).

4-(5-phenyl-1, 3, 4-oxadiazol-2-yl) pyridine (5a)

IR(KBr) in cm^{-1}:3054(C-H of aromatic ring),1626(C=N str),1042(C-O-C str); ^{1}HNMR($CDCl_3$): δ7.62-8.66(m,4H,Ar-H in pyridine),6.62-7.24(m,5H,Ar-H);MS(m/z):224(M+1).

4-[5(4-chlorophenyl)-1, 3, 4-oxadiazol-2-yl] pyridine (5b)

IR(KBr) in cm^{-1}:3048(C-H of aromatic ring), 1623(C=N str), 1039(C-O-C str), 676(C-Cl str); ^{1}HNMR($CDCl_3$): δ7.64-8.67(m,4H,Ar-H in pyridine), 6.63-7.22(m,4H,Ar-H); MS(m/z):258(M+1).

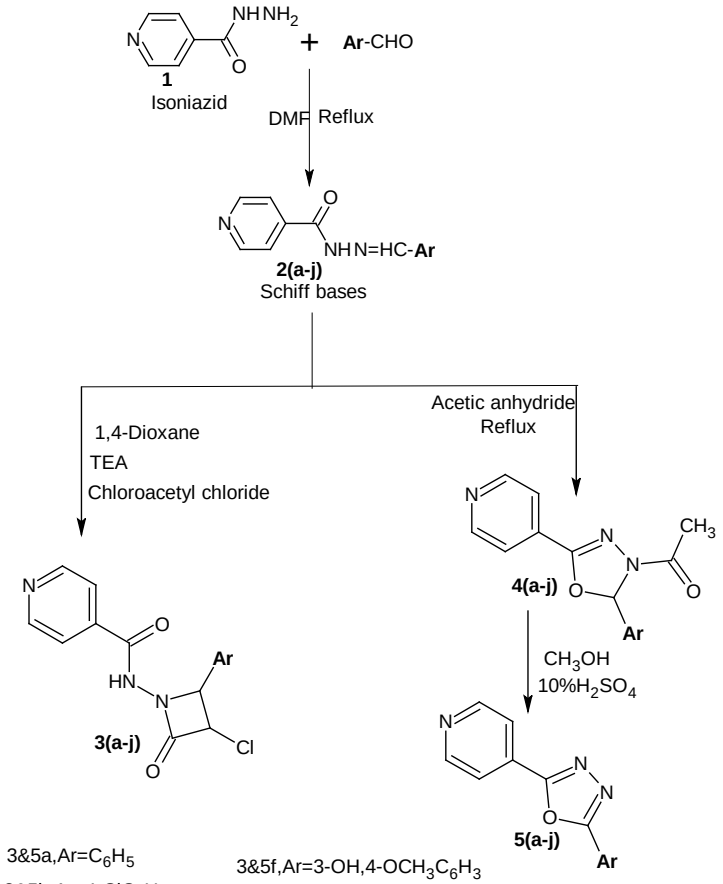
4-[5-(2-furyl)-1, 3, 4-oxadiazol-2-yl] pyridine (5h)

IR(KBr) in cm^{-1}:3054(C-H of aromatic ring),1628(C=N str),1076(C-O-C str); ^{1}HNMR($CDCl_3$): δ7.64-8.65(m,4H,Ar-H in pyridine),6.42-7.23(m,3H,Ar-H);MS(m/z):213(M^+).

Antibacterial activity[19]

Antibacterial activity of all the test compounds was determined by Agar well diffusion method, as recommended by the national committee for clinical laboratory standards against Gram-positive bacteria such as *Staphylococcus aureus*(NCIM 2079) & *Bacillus subtilus* (NCIM 2063) and two Gram-negative bacteria *Escherichia coli*(NCIM 2068) & *pseudomonas aeruginosa*(NCIM 2200) at 100µg/mL concentration in dimethyl sulfoxide(DMSO) solvent.

The results were compared with standard drug ampicillin. The fresh culture of bacteria are obtained by inoculating bacteria into nutrient broth media and incubated at 37^{0}C for 24hr. This culture mixed with nutrient agar media was poured into petridishes under aseptic conditions. After solidification of media, bores are made by using sterile cork borer (8mm diameter). Into these cups standard drug and synthesized drugs are introduced, the plates were placed in refrigirator at10^{0}c for proper diffusion of drugs into media. After 2hr, the petriplates were transferred to incubator and maintained at 37±2^{0}C for 24hr. After the incubation period, the petriplates were observed for zone of inhibition. The results are evaluated by comparing the zone of inhibition shown by the synthesized compounds with standard drug.



Scheme-1

RESULTS AND DISCUSSION

The required synthon, Schiff bases 2(a-j) were prepared by condensation of isoniazid(1) with substituted aromatic aldehydes in DMF. The compounds 2(a-j) when reacted with chloroacetyl chloride in 1,4-dioxane in the presence of triethylamine gave N-(3-chloro-2-oxo-4-substituted phenylazetidin-1-yl) isonicotinamide derivatives 3(a-j).The analytical data were given in Table-1.

Compounds2 (a-j) on reaction with acetic anhydride resulted N-acetyl-1, 3, 4 oxadiazolines 4(a-j). The compounds 4(a-j) on treatment with sulphuric acid in methanol afforded 4-(5-substituted phenyl-1, 3, 4-oxadiazol-2-yl) pyridine derivatives 5(a-j) in good yields. The analytical data of these compounds were given in Table-2. The characterization of newly synthesized compounds was based on their physical, spectral and analytical data. The synthesized compounds were evaluated for their antibacterial activity. The screening data are shown in Table-3&Table-4 indicated that the compounds 3b, 3j, 5b and 5j showed significant antibacterial activity. Remaining compounds were found to possess moderate activity against gram+ve and gram-ve strains when compared with standard drug ampicillin. With further molecular modification and manipulation of these compounds, several other promising bioactive molecules can be developed in future.

Table 1: Analytical data of N-(3-chloro-2-oxo-4-substituted phenylazetidin-1-yl) isonicotinamide derivatives 3(a-j)

Cpd.code	Mol.formula	Mol.Wt	M.P(^{0}C)	R_f value	Yield (%)	Elemental analysis (%) Calcd.(found)		
						C	H	N
3a	$C_{15}H_{12}ClN_3O_2$	301	184-186	0.72	78	59.71 (59.69)	4.01 (3.98)	13.93 (13.89)
3b	$C_{15}H_{12}Cl_2N_3O_2$	336	192-193	0.62	76	53.59 (53.52)	3.30 (3.26)	12.50 (12.43)
3c	$C_{15}H_{11}ClN_4O_4$	346	185-186	0.80	79	51.96 (51.92)	3.20 (3.18)	16.16 (16.11)
3d	$C_{16}H_{14}ClN_3O_3$	331	186-187	0.62	75	57.93 (57.89)	4.25 (4.21)	12.64 (12.61)
3e	$C_{17}H_{16}ClN_3O_4$	361	189-190	0.59	77	56.44 (56.39)	4.46 (4.40)	11.61 (11.59)
3f	$C_{16}H_{14}ClN_3O_4$	347	183-184	0.76	74.5	55.26 (55.21)	4.06 (4.02)	12.08 (12.03)
3g	$C_{17}H_{17}ClN_4O_2$	344	182-183	0.71	76.5	59.22 (59.19)	4.97 (4.92)	16.25 (16.19)
3h	$C_{13}H_{10}ClN_3O_3$	291	193-194	0.56	73	53.53 (53.49)	3.46 (3.41)	14.41 (14.39)
3i	$C_{17}H_{14}ClN_3O_2$	327	198-199	0.81	75.5	62.30 (62.27)	4.31 (4.26)	12.82 (12.78)
3j	$C_{17}H_{13}ClN_4O_2$	340	191-192	0.72	79.5	59.92 (59.88)	3.85 (3.82)	16.44 (16.40)

Table 2: Analytical data of 4-(5-substituted phenyl-1,3,4-oxadiazol-2-yl)pyridine derivatives 5(a-j)

Cpd. code	Mol. formula	Mol. Wt	M.P(^{0}C)	R_f value	Yield (%)	Elemental analysis (%) Calcd. (found)		
						C	H	N
5a	$C_{13}H_9N_3O$	223	189-191	0.70	77	69.95 (69.89)	4.06 (4.01)	18.82 (18.78)
5b	$C_{13}H_8ClN_3O_2$	257	182-184	0.63	74	60.60 (60.56)	3.13 (3.10)	16.31 (16.23)
5c	$C_{13}H_8N_4O_3$	268	185-186	0.80	78.5	58.21 (58.18)	3.01 (2.97)	20.89 (20.85)
5d	$C_{14}H_{11}N_3O_2$	253	178-179	0.64	79	66.40 (66.36)	4.38 (4.33)	16.59 (16.53)
5e	$C_{15}H_{13}N_3O_3$	283	183-184	0.69	76	63.60 (63.55)	4.63 (4.58)	14.83 (14.77)
5f	$C_{14}H_{11}N_3O_3$	269	195-197	0.73	73.5	62.45 (62.39)	4.12 (4.08)	15.61 (15.57)
5g	$C_{15}H_{14}IN_4O$	266	180-181	0.81	75.5	67.65 (67.60)	5.30 (5.26)	21.04 (20.06)
5h	$C_{11}H_7N_3O_2$	213	179-180	0.76	72	61.97 (61.92)	3.31 (3.27)	19.71 (19.66)
5i	$C_{15}H_{11}N_3O$	249	190-192	0.71	76.5	72.28 (72.23)	4.45 (4.41)	16.86 (16.82)
5j	$C_{15}H_{10}N_4O$	262	186-188	0.77	74.5	68.69 (68.62)	3.84 (3.79)	21.36 (21.32)

Table 3: Antibacterial activity of N-(3-chloro-2-oxo-4-substituted phenylazetidin-1-yl) isonicotinamide derivatives 3(a-j)

Comp. Code	Zone of inhibition (Diameter in mm)			
	Staphylococcus aureus	Bacillus subtilus	Escherichia coli	pseudomonas aeruginosa
3a	18	16	17	16
3b	23	21	24	22
3c	19	15	16	13
3d	14	12	15	14
3e	18	16	14	15
3f	16	19	17	18
3g	17	15	14	16
3h	15	14	16	17
3i	19	18	17	15
3j	22	23	23	21
Ampicillin	25	24	27	24

Table 4: Antibacterial activity of 4-(5-substituted phenyl-1,3,4-oxadiazol-2-yl)pyridine derivatives 5(a-j).

Comp. Code	Zone of inhibition (Diameter in mm)			
	Staphylococcus aureus	**Bacillus subtilus**	**Escherichia coli**	**pseudomonas aeruginosa**
5a	17	14	15	16
5b	23	22	24	21
5c	18	16	14	13
5d	15	13	15	16
5e	17	15	16	14
5f	18	17	15	17
5g	16	14	13	12
5h	15	16	12	14
5i	19	17	18	15
5j	21	22	23	22
Ampicillin	25	24	27	24

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